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SUBSTITUTION MODE OF THE AMIDE FRAGMENT IN SOME NEW N-{ω-[4-(2-METHOXYPHENYL)PIPERAZIN--1-YL]ALKYL}PYRID-2(1H)-ONES AND THEIR 5-HT_{1A}/5-HT_{2A} ACTIVITY

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Substitution mode of the amide fragment in some new N-{ω-[4-(2-methoxyphenyl)piperazin-1-yl]alkyl}pyrid-2(1H)-ones and their 5-HT_{1A}/5-HT_{2A} activity. M.H. PALUCHOWSKA, R. BUGNO, S. CHARAKCHIEVA--MINOL, A.J. BOJARSKI, A. WESOŁOWSKA. Pol. J. Pharmacol., 2001, 53, 369–376.

A series of ω-[4-(2-methoxyphenyl)piperazin-1-yl]alkyl derivatives with terminal pyrid-2(1H)-one fragments was synthesized and evaluated for their 5-HT_{1A} and 5-HT_{2A} activity. Enlargement of the aromatic amide system by its substitution with phenyl and/or *p*-methoxyphenyl in positions 4, 5 and/or 6, as well as modification of an aliphatic spacer allowed us to better understand structure-activity relationships in that group of compounds. The results of *in vitro* and *in vivo* experiments showed that only unsubstituted (**1b**) and monosubstituted (**2b**–**4b**) derivatives with the tetramethylene spacer demonstrated high 5-HT_{1A} receptor affinity (K_i = 15–40 nM) and 5-HT_{1A}/5-HT_{2A} selectivity; they exhibited features of 5-HT_{1A} antagonists. Those results suggested that the mode of substitution of the terminal amide moiety in the tested tetramethylene arylpiperazines was not significant for their 5-HT_{1A} receptor activity. Conformational analysis calculations indicated that despite its great capacity for adaptation at 5-HT_{1A} receptor site, an aryl substituent in position 4 in the pyrid-2(1H)-one ring destabilized the ligand-5-HT_{1A} receptor complex formation in the case of trimethylene derivatives. Diarylsubstituted derivatives (**5a**–**8a** and **5b**–**8b**) were characterized by a low 5-HT_{2A} affinity (K_i > 446 nM) regardless of the spacer length, while those with the tetramethylene aliphatic chain had a higher 5-HT_{2A} affinity than the remaining investigated compounds.

Key words: *5-HT_{1A} receptor antagonists, 5-HT_{2A}/5-HT_{1A} selectivity, pyrid-2(1H)-one derivatives*

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